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WO 01/05395 A1

(54) Title: SELECTIVE INHIBITION OF CYCLOOXYGENASE-2

(57) Abstract: Disclosed is a method for selectively inhibiting cyclooxygenase 2 in an animal having a cyclooxygenase 2 activity by delivering into the animal an amount of a conjugated linoleic acid effective to reduce cyclooxygenase 2 activity in the animal.

SELECTIVE INHIBITION OF CYCLOOXYGENASE-2

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

5 STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH
OR DEVELOPMENT

To be determined.

BACKGROUND OF THE INVENTION

10 Inflammatory reactions and associated pain can be induced by prostaglandins. Inflammation can be reduced by inhibiting prostaglandin biosynthesis. Most non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit prostaglandin synthesis by inhibiting cyclooxygenase, a key regulated enzyme in synthesis of 20 carbon eicosenoids, including prostaglandin E2 (PGE₂), from 15 arachidonic acid. However, complete inhibition of prostaglandin synthesis is disfavored because prostaglandins also beneficially maintain the digestive tract lining. In the absence of prostaglandins, a 20 propensity for ulcers and similar digestive problems can develop. This is particularly problematic for people suffering from conditions such as arthritis, the treatment of which generally requires long-term use of relatively large doses of anti-inflammatory agents.

25 The cyclooxygenase enzymes are reviewed by Williams, C. S. and R. N. DuBois, "Prostaglandin endoperoxide synthase: Why two isoforms?" Am. J. Physiol. 270 (Gastrointest. Liver Physiol. 33):G393-G400 (1996), incorporated herein by reference in its entirety. Briefly, 30 cyclooxygenase exists in at least two different enzyme isoforms (Simmons et al., P.N.A.S. U.S.A. 86:1178-1182

(1989)), designated Cox-1 and Cox-2. Cox-1 is involved in synthesizing housekeeping prostaglandins that function to maintain the digestive tract lining. In contrast, Cox-2 catalyzes the synthesis of prostaglandins that cause 5 inflammation and pain, but does not appear to catalyze housekeeping prostaglandins. Both Cox-1 and Cox-2 are involved in producing precursors for several prostanoids including PGE₂.

Cox-1 is expressed constitutively at relatively stable 10 levels in many tissues, whereas Cox-2 expression can be induced by a variety of chemicals, including, but not limited to, lipopolysaccharides, phorbol esters, interleukin-1, tumor necrosis factor, human chorionic gonadotropin, and platelet activating factor. As a result 15 of this distinction, one can characterize the relative contribution of each isoform to the overall PGE₂ level by comparing basal PGE₂ levels to the levels after induction.

Because existing drugs that bind both Cox-1 and Cox-2 can cause significant undesired gastric side effects, 20 considerable attention has been directed toward developing pain relief medications that specifically inhibit Cox-2 enzyme activity without affecting Cox-1 enzyme activity. Recently, the Food and Drug Administration approved one 25 such medication, Celebrex, only for the treatment of arthritis pain, pending further studies. Preliminary results suggest that Celebrex provides pain relief and reduces inflammation without causing stomach problems. Unfortunately, Celebrex is expensive.

Accordingly, there is currently a strong interest in 30 developing pharmaceuticals and therapies that reduce inflammation and provide pain relief without causing associated stomach problems.

Conjugated linoleic acid reduces liver and serum PGE₂ 35 levels in rats fed a diet containing 1% CLA (Sugano, et al. Nutritional Biochem. 8:38-43, 1997). Liu et al. (Cancer Lett. 127:15-22, 1998) suggested that CLA inhibits PGE₂ synthesis by cyclooxygenase by competing with the enzyme's

substrate, arachidonic acid. It was not known whether conjugated linoleic acids inhibit both Cox-1 and Cox-2.

BRIEF SUMMARY OF THE INVENTION

The present invention is a method of selectively 5 inhibiting Cox-2 in an animal expressing Cox-2, the method comprising the step of administering to the animal a conjugated linoleic acid in an amount effective to selectively reduce the activity of Cox-2 without substantially reducing the activity of Cox-1. Selective 10 reduction of Cox-2 activity can be assessed by comparing levels of PGE₂ before and after inducing Cox-2 expression, as described herein.

It is an object of the present invention to 15 selectively reduce the activity of Cox-2 enzyme without substantially reducing the activity of Cox-1.

It is an advantage of the present invention that conjugated linoleic acid is generally regarded as safe and non-toxic when administered to animals and humans.

It is another advantage of the present invention that 20 conjugated linoleic acid can be obtained and used without prescription.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Fig. 1 shows the magnitude and time course of 25 prostaglandin E₂ (PGE₂) release from superfused trachea of sensitized guinea pigs fed a control diet (diamonds) or a diet containing 0.25% CLA (squares) before (collection period 0) and after (periods 1-8) antigen challenge.

Figs. 2A-2C shows the release of PGE₂ from lung (A), 30 bladder (B), and trachea (C) tissue from sensitized guinea pigs with or without (basal) antigen challenge.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have recognized, and disclose herein, 35 that conjugated linoleic acid (CLA) selectively inhibits Cox-2 enzyme activity without significantly reducing Cox-1

enzyme activity in animals administered an amount of CLA effective to inhibit Cox-2 enzyme activity. This observation was not previously noted, and permits advantageous therapeutic interventions that satisfy a 5 stated object of the present invention. The observation is important because the housekeeping functions of Cox-1 are maintained without adverse effect, while the inflammatory response and pain associated with Cox-2-directed prostaglandin synthesis can be controlled.

10 Accordingly, one aspect of the present invention is a method for selectively inhibiting cyclooxygenase 2 (Cox-2) in an animal expressing Cox-2, the method comprising the step of administering to the animal an amount of at least one conjugated linoleic acid isomer effective to 15 selectively reduce the activity of Cox-2 without substantially affecting cyclooxygenase 1 (Cox-1) activity. The absolute percent reduction of Cox-2 activity is less critical than the *in vivo* effects caused by reduced Cox-2 activity. What is important is that CLA inhibits Cox-2 20 activity to an extent sufficient to reduce inflammation, without causing stomach problems.

The effect is most readily studied in an *ex vivo* model system, although by carefully selecting an appropriate model system, namely guinea pigs, one can reasonably 25 predict success in mammals, including humans and domesticated animals such as farm animals and pets. In the model system, Cox-2 activity is preferably reduced by at least about 10% in tissue from animals fed a diet containing CLA. More preferably, Cox-2 activity is reduced 30 by 20% or even 50% or more. At the same time, Cox-1 activity is reduced insignificantly.

The effect of CLA on cyclooxygenase activity can also be expressed as the percentage ratio of the Cox-2:Cox-1 reduction. Preferably, the percentage ratio is maximized 35 so as to afford effective pain relief and reduced inflammation, without interfering with the maintenance functions of Cox-1. Preferably, this ratio is at least

about 2:1. More preferably, this ratio is at least about 20:1, or even about 50:1.

In this application "conjugated linoleic acid" or "CLA" means an unsaturated fatty acid having 18 carbons and two conjugated double bonds, the fatty acid being selected from the group consisting of 18:2(9c,11t), 18:2(9t,11c), 18:2(10c,12t) and 18:2 (10t,12c), and also including bioactive esters and salts thereof, and mixtures thereof.

5 The CLA may be administered by any convenient means.

10 Preferably, the conjugated linoleic acid is delivered orally in a capsule, tablet, or chewable form comprising conjugated linoleic acid and a pharmaceutically acceptable ingestible carrier. It is envisioned that the CLA can be administered orally for timed-release delivery.

15 Alternatively, the CLA may be formulated for intravenous, intramuscular, transdermal, or transmucosal administration. Since CLA is generally regarded as safe, the precise amount of CLA administered is not considered critical, as long as it is sufficient to achieve a stated object of the

20 invention. For example, if fed to an animal, an appropriate amount of CLA in the diet is in the range of 0.1% to 5% by weight, preferably 0.2% to 0.5% by weight in the diet. If administered by another route, CLA can be effectively administered at a dosage ranging from about 1

25 mg/kg to about 1000 mg/kg body weight of the animal or higher. This corresponds to about 0.1 g/day to about 40 g/day for a person weighing 45 kg.

In the following non-limiting examples, Cox-1 and Cox-2 activity were measured indirectly by monitoring the levels of PGE₂ released from excised tissue of sensitized animals fed CLA or CLA-free diets, in the presence or absence of an inducing antigenic challenge. The examples demonstrate that the method of the present invention is effective in reducing Cox-2 directed PGE₂ production in guinea pigs, a preferred model system for evaluating immune 30 and inflammatory responses in mammals, including humans.

35 Since the chemical structure of COX-2 substrates are the

same in all animal species, it is reasonably predicted from these trials that the method of the present invention will achieve selective inhibition of Cox-2 in any animal having the Cox-2 isoform, including in humans.

5 PGE₂ levels were measured in excised tissue from guinea pigs fed (or not fed) CLA and sensitized to an antigen using tracheal superfusion or tissue baths containing lung, bladder, or tracheal tissue. One wishing to monitor Cox-2 response to CLA could alternatively
10 measure the amount of Cox-2 protein or Cox-2 mRNA formed in appropriate tissues.

In the absence of an inducing antigen challenge, tissue from CLA-fed animals exhibits only slight decreases in PGE₂ production, relative to animals fed a CLA-free
15 control diet. In contrast, in tissue subjected to inducing antigen challenge, much greater PGE₂ reduction was observed in tissue from animals fed CLA in the diet than in tissue from animals fed CLA-free diets. These results suggest that the CLA specifically inhibits the inducible Cox-2
20 enzyme activity to a much greater extent than it inhibits the constitutively expressed Cox-1 enzyme activity.

The invention will be better understood upon consideration of the following non-limiting examples.

EXAMPLE 1

25 Superfusion

Diets and sensitization

Three experiments were completed using identical conditions in each of the three experiments, except where otherwise noted. Female Hartley guinea pigs (Harlan,
30 Madison, WI) weighing 200-350g were housed in a temperature- and humidity-controlled room with a 12 hour light-dark cycle. The guinea pigs were randomly divided into two diet groups (n=6 guinea pigs/treatment in experiments 1 and 3, n=3 guinea pigs/treatment in
35 experiment 2). One of the two groups received a control

diet which comprised a standard guinea pig diet (Harlan-Teklad) supplemented with 0.25% corn oil (experiment 1) or 0.25% linoleic acid (Nu-Check prep; experiments 2 and 3). The second set of animals in each experiment received a 5 standard guinea pig diet (Harlan-Teklad) supplemented with 0.25% conjugated linoleic acid (CLA) synthesized from linoleic acid by previously described methods (Chin, et al., J. Food Comp. and Anal. 5:185-197 (1992)).

The guinea pigs were given free access to the 10 experimental diets for at least 1 week prior to and during active sensitization to chicken egg ovalbumin (OVA, Sigma) antigen. Guinea pigs were sensitized with an initial intraperitoneal (IP) injection of 50 ug OVA in PBS with aluminum hydroxide followed two weeks later by a 15 subcutaneous injection (flank) of 200 ug OVA in PBS emulsified with equal volume of Incomplete Freund's Adjuvant. The animals were sacrificed 4 days after the second injection of OVA by an intraperitoneal injection of sodium pentobarbital.

20 Tracheal Superfusion

The tracheas of the sensitized guinea pigs were removed shortly after the animals were killed and transferred to petri dishes containing a bicarbonate buffered physiological saline solution (PSS) (118 mM NaCl, 25 1.0 mM NaH₂PO₄, 4.7 mM KCl, 2.5 mM CaCl₂, 0.5 mM MgCl₂, 11 mM glucose, and 25 mM NaHCO₃). Excess tissue was removed from the tracheas, taking care to avoid stretching or abrading the tracheas. Each trachea was cut longitudinally at a 45° angle into a spiral (Constantine, 1965) and 30 suspended in an air-filled, water-jacketed tissue chamber maintained at 37°C. The tracheas were superfused at a rate of 2.2 ml/min with PSS (37°C, gassed with 95% O₂ and 5% CO₂) while being kept at a tension of 5g for an equilibration period of 90 minutes. Changes in tensions were measured 35 with FT 03 electrical force transducers and plotted with a Grass polygraph. Following equilibration, tracheas were

challenged by continuously superfusing PSS containing 0.01 mg/ml OVA. Superfusates were continually collected in 90 sec intervals beginning 90 sec before antigen challenge (designated collection period 0) and placed at 4°C. Peak 5 changes in tracheal tensions were determined for each 90 sec collection period. Superfusates were analyzed for histamine and PGE₂ content. Following antigen challenge, tracheas were continuously superfused with PSS containing 10⁻⁵ carbachol (carbamylcholine chloride, Sigma) to produce 10 a maximum contractile response. Following carbachol contractions, tracheas were weighed, minced with scissors and homogenized in 0.4 N perchloric acid, and placed in a boiling water bath for 10 min for to extract residual histamine.

15 Mediator analysis

The PGE₂ content of superfusates was determined using the room temperature protocol of an enzyme immunoassay system (Amersham Life Science). The sensitivity of this assay is 40 pg/ml. Cross reactivity with PGE₁, PGF_{2a}, 6-20 keto-PGF_{1a}, and arachidonic acid is 25%, 0.04%, <0.1%, and <0.001%, respectively.

Results

Fig. 1 shows the amount of PGE₂ released from tracheas of CLA-fed and CLA-free animals before and after induction 25 of Cox-2 activity. Before induction (collection period 0), the CLA-fed and CLA-free animals both produce low levels of PGE₂, although CLA-fed animals produce slightly less PGE₂ than CLA-free animals, possibly reflecting an inhibition of endogenous low level Cox-2 activity. After induction 30 (collection periods 1-8), CLA-fed animals consistently produce less PGE₂ than CLA-free animals, thereby demonstrating that an increase in PGE₂ synthesis attributable to induction of Cox-2 can be substantially reduced by administering CLA that inhibits Cox-2 activity.

Example 2
Tissue Bath Data

Diets and sensitization

5 The diet and sensitization protocols for two tissues
bath experiments were essentially as described above for
the superfusion experiments, with n=3 guinea pigs/treatment
in experiment 1 and n=6 guinea pigs/treatment in experiment
2. The control diets contained 0.25% safflower oil, and
CLA-90 (Natural) was used for CLA diets.

10 Tissue bath experiments

Following sensitization and sacrifice as described
above, the lungs, trachea, and bladder were removed from
the guinea pigs. Each tissue was weighed, placed in 37°C
PSS baths, and allowed to equilibrate in the baths for at
15 least one hour. The OVA antigen was added to the baths,
and after one hour baths were collected for analysis of
PGE₂ and LTB₄ release. Basal levels of release were
determined from bath buffer collected prior to antigen
challenge.

20 Mediator analysis

The PGE₂ and LTB₄ contents of tissue bath samples were
analyzed using enzyme immunoassay systems (Amersham Life
Science). The PGE₂ assay was as described above. The
sensitivity of the LTB₄ assay is 6 pg/ml, and the cross-
25 reactivities with 20-OH-LTB₄, 6-trans-LTB₄, LTC₄, LTD₄, 5-
hydroxyeicosatetraenoic acid (5-HETE), and 12-HETE are 2.0,
25.5, 0.011, 0.010, 0.008, and 0.034, respectively.

Results

Figs. 2A-2C shows the amount of PGE₂ released from lung
30 (Fig. 2A), bladder (Fig. 2B) and trachea (Fig. 2C) of CLA-
fed and CLA-free animals before and after induction of Cox-
2 activity. Before induction (basal level), the CLA-fed
and CLA-free animals both produce low levels of PGE₂,

although CLA-fed animals produce slightly less PGE₂ than CLA-free animals, possibly reflecting an inhibition of endogenous low level Cox-2 activity. After induction (challenge level), CLA-fed animals consistently produce 5 less PGE₂ than CLA-free animals, thereby demonstrating that an increase in PGE₂ synthesis attributable to induction of Cox-2 can be substantially reduced by administering CLA that inhibits Cox-2 activity.

10 All publications cited in the specification are incorporated by reference.

The present invention is not limited to the exemplified embodiments, but is intended to encompass all such modifications and variations as come within the scope of the following claims.

CLAIMS

WE CLAIM:

1. A method for selectively inhibiting cyclooxygenase 2 activity in an animal having cyclooxygenase 2 activity, comprising the step of:
 - 5 administering to the animal an amount of a conjugated linoleic acid effective to reduce the activity of cyclooxygenase 2.
2. The method of claim 1, wherein the administering step comprises a method selected from the group consisting of oral delivery, intramuscular injection, intravenous injection, transdermal delivery, and transmucosal delivery.
 - 10
3. The method of claim 1, wherein the administering step comprises oral delivery.
 - 15
4. The method of claim 1, wherein the animal is a human.
 - 20
5. The method of claim 1, wherein the conjugated linoleic acid is selected from the group consisting of an 18:2(9c,11t) isomer, an 18:2(9t,11c) isomer, an 18:2(10c,12t) isomer, an 18:2 (10t,12c) isomer, a bioactive ester thereof, a salt thereof, and a mixture thereof.
6. The method of claim 1, wherein the CLA is delivered in a dosage of between about 1 mg/kg and 1000 mg/kg body weight of the animal.

7. A method for reducing inflammation in an animal comprising the step of delivering into the animal an amount of a conjugated linoleic acid effective to reduce the inflammation without causing gastric irritation.

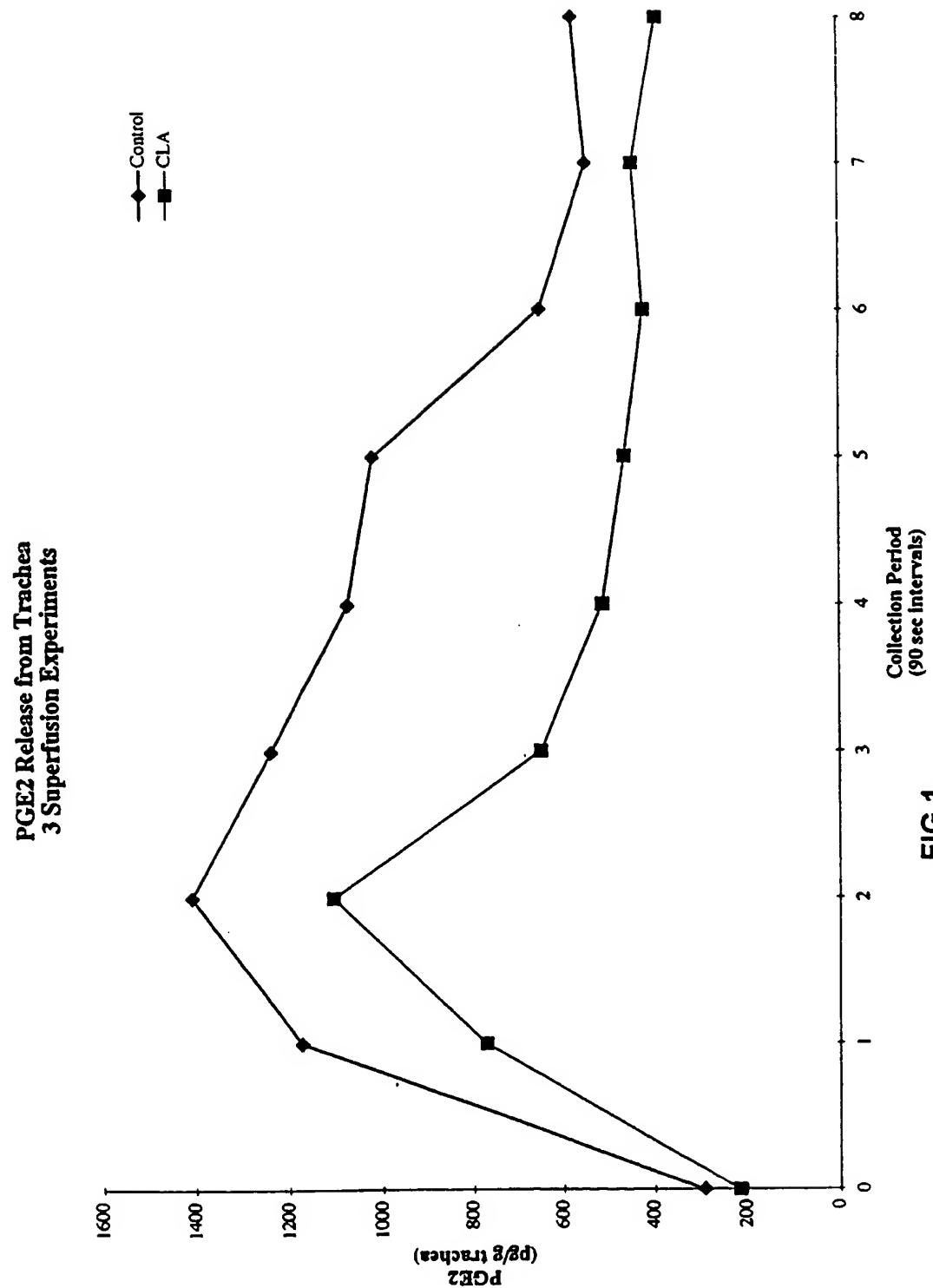


FIG 2A

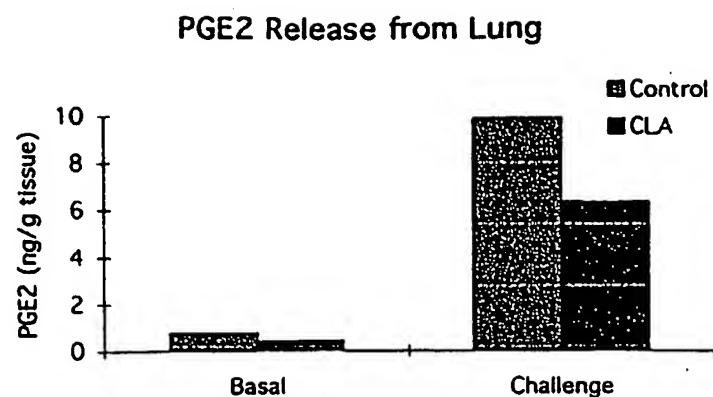


FIG 2B

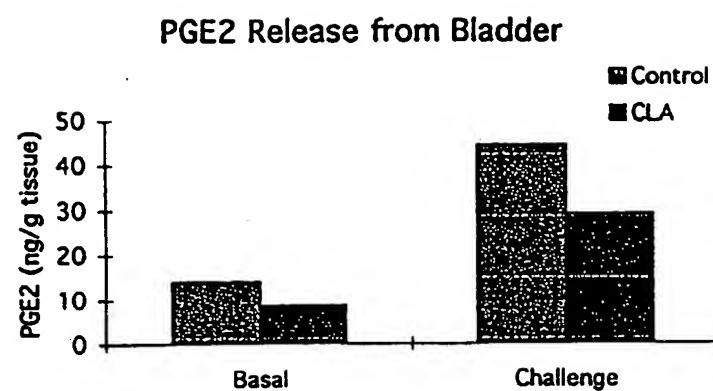
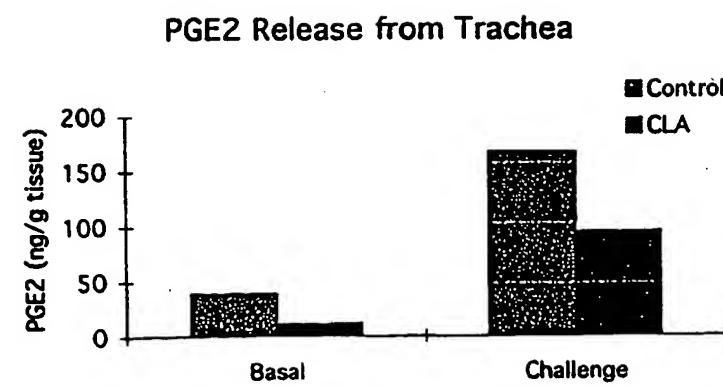


FIG 2C



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/07824

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/231 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, MEDLINE, EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CANCERLIT, AIDSLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 585 400 A (COOK MARK E ET AL) 17 December 1996 (1996-12-17) column 1, line 42 - line 62 column 2, line 9 - line 24 column 2, line 46 - line 61 column 3, line 11 -column 4, line 42 example 1 figure 2 --- TRUITT A ET AL: "Antiplatelet effects of conjugated linoleic acid isomers." BIOCHIMICA ET BIOPHYSICA ACTA, (1999 MAY 18) 1438 (2) 239-46. , XP000852565 abstract page 240, column 1, paragraph 2 page 245, column 1, paragraph 3 -column 2, paragraph 2 --- -/--	1-7
X		1,4,5

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

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30 June 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KAVANAUGH C J ET AL: "Effect of dietary conjugated linoleic acid on phorbol ester-induced PGE2 production and hyperplasia in mouse epidermis." NUTRITION AND CANCER, (1999) 33 (2) 132-8.</p> <p>XP000920912 abstract page 132, column 2, paragraph 2 - paragraph 3 page 133, column 1, paragraph 2 page 135, column 1, paragraph 2 figure 1 page 137, column 1, paragraph 2 page 137, column 1, paragraph 6 -column 2, paragraph 1 ---</p>	1-6
X	<p>TUREK, JOHN J.; LI, YONG; SCHOENLEIN, INGRID A.; ALLEN, KEN G. D.; WATKINS, BRUCE A.: "Modulation of macrophage cytokine production by conjugated linoleic acids is influenced by the dietary n-6:n-3 fatty acid ratio" J. NUTR. BIOCHEM. (1998), 9(5), 258-266, XP000920933 abstract page 258, column 2, paragraph 2 -page 259, column 1, paragraph 1 figure 1 page 263, column 1, paragraph 2 -column 2, paragraph 1 ---</p>	1-6
X	<p>CHEMICAL ABSTRACTS, vol. 128, no. 12, 23 March 1998 (1998-03-23) Columbus, Ohio, US; abstract no. 140104, KIM, SO-HEE ET AL: "Effects of conjugated linoleic acid (CLA) on the growth of tumor cells and the production of interleukin-1 and interleukin-2" XP002141453 abstract & HAN'GUK SIKP'UM YONGYANG KWAHAK HOECHI (1997), 26(5), 972-977 , ---</p>	1,4,7

INTERNATIONAL SEARCH REPORT

International Application No	
PCT/US 00/07824	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MCCARTY, MARK F.: "Downregulation of macrophage activation by PPAR.gamma. suggests a role for conjugated linoleic acid in prevention of Alzheimer's disease and atherosclerosis."</p> <p>J. MED. FOOD (1999), VOLUME DATE 1998, 1(3), 217-226, XP000920842</p> <p>abstract</p> <p>page 219, column 1, paragraph 3</p> <p>page 220, column 2, paragraph 3</p> <p>page 221, column 2, paragraph 4</p> <p>page 222, column 1, paragraph 2</p> <p>---</p>	1,4,7
X	<p>WHIGHAM L D; HIGHER A J; PARIZA M W; COOK M E : "Influence of dietary conjugated linoleic acid on release of PGE2 and LTB4 from guinea pig lung, trachea, and bladder."</p> <p>FASEB JOURNAL,</p> <p>vol. 13, no. 4 Part 1,</p> <p>12 March 1999 (1999-03-12), page A587</p> <p>XP000914685</p> <p>the whole document</p> <p>---</p>	1-6
X	<p>WHIGHAM L D; COOK E B; STAHL J L; SABAN R; PARIZA M W; COOK M E: "Conjugated linoleic acid reduced antigen-induced prostaglandin E2 release from sensitized tracheas."</p> <p>FASEB JOURNAL,</p> <p>vol. 12, no. 5 Supp. S,</p> <p>20 March 1998 (1998-03-20), page 4749</p> <p>XP000914686</p> <p>the whole document</p> <p>---</p>	1-3,5,6
X	<p>WO 99 32105 A (DCV INC DOING BUSINESS AS BIO) 1 July 1999 (1999-07-01)</p> <p>abstract</p> <p>page 2, line 11 - line 23</p> <p>page 9, paragraph 7 - paragraph 8</p> <p>---</p>	7
P,X	<p>EP 0 955 047 A (UNIV GEORGE WASHINGTON)</p> <p>10 November 1999 (1999-11-10)</p> <p>the whole document</p> <p>---</p> <p>-/-</p>	1-6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WALLACE JOHN L; CHAPMAN KEVIN; MCKNIGHT WEBB : "Limited anti-inflammatory efficacy of cyclo-oxygenase-2 inhibition carrageenan-airpouch inflammation." BRITISH JOURNAL OF PHARMACOLOGY , vol. 126, no. 5, March 1999 (1999-03), pages 1200-1204, XP000920911 abstract page 1200, column 1, paragraph 1 page 1202, column 2, paragraph 5 page 1203, column 2, paragraph 2</p> <p>-----</p>	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-6 relate to the treatment of a disease which actually is not well-defined. The use of the definition "selectively inhibiting cyclooxygenase 2 activity" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the disease specifically mentioned in claim 7, namely inflammation, with due regard to the general idea underlying the application.

Claims searched partially: 1-6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/07824

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		EP 0883681 A		16-12-1998
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EP 0955047 A	10-11-1999	NONE		

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